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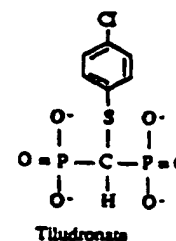
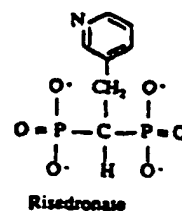
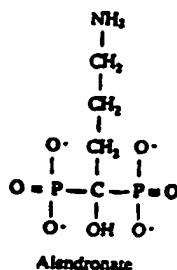
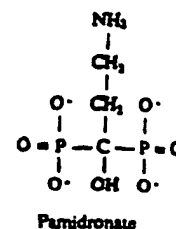
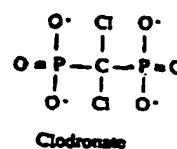
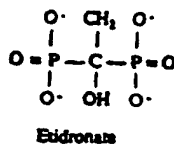
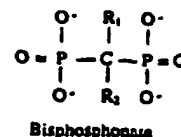
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(54) Title: COMPOSITIONS AND METHODS FOR THE TREATMENT OF METABOLIC BONE DISORDERS AND BONE METASTASES

(57) Abstract

The present invention is drawn to methods and compositions useful for targeting and treating target tissues affected by or involved in metabolic bone disorders and bone metastases with photodynamic therapy (PDT) in a mammalian subject. The compositions are bisphosphonates, pyrophosphates or bisphosphonate-like compounds conjugated to photosensitive agents which are optionally further conjugated to ligands which are target tissue specific antibodies, peptides or polymers. The methods of PDT treatment utilize these compositions to target the tissues or cells of a mammalian subject to be treated. The methods comprise irradiating at least a portion of the subject with light at a wavelength absorbed by said photosensitizing agent that under conditions of activation during photodynamic therapy using a relatively low fluence rate, but an overall high total fluence dose results in minimal collateral tissue damage.



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COMPOSITIONS AND METHODS FOR THE TREATMENT OF
METABOLIC BONE DISORDERS AND BONE METASTASES

TECHNICAL FIELD OF THE INVENTION

5 This invention relates generally to the field of medicine and
pharmacotherapeutics with photosensitizing agents or other energy activated agents.
Specifically, this invention relates to methods, compounds, compositions and kits
useful for targeting and treating metabolic bone disorders and bone metastases with
photodynamic therapy (PDT).

BACKGROUND OF THE INVENTION

10 A balanced physiological process of bone resorption, mediated by osteoclasts,
and new bone formation, mediated by osteoblasts, maintains normal skeletal integrity.
Enhanced bone resorption, however, is typical of metabolic bone disorders such as
15 Paget's Disease, malignant hypercalcemia, osteoporosis and bone metastases. Paget's
Disease is characterized by enhanced osteoclastic activity followed by abnormal
osteoblast proliferation and increased bone formation. Hypercalcemia, a frequent
complication of breast, prostate, lung and hematopoietic malignancies, may result
from the direct lytic effect of tumor cells on bone, osteoclast activation by paracrine
20 factors released from tumor cells, or increased renal calcium. Bone metastases are
another frequent complication of breast, prostate, lung and hematopoietic
malignancies. Osteoporosis is caused by either increased osteoclastic activity and
accelerated bone resorption or reduced osteoclastic activity.

25 Adverse complications of metastatic bone disorders such as these include pain,
pathologic fractures, spinal cord compression, hypercalcemia and immobility.
Current therapies are palliative and include radiotherapy, radiopharmaceuticals,
surgery, endocrine therapy, chemotherapy and bisphosphonates.

30 Bisphosphonates are synthetic analogs of naturally occurring inorganic
pyrophosphates and have been used for many years in the treatment of Paget's
Disease and hypercalcemia because like inorganic pyrophosphates, bisphosphonates
bind to hydroxyapatite crystals in mineralized bone matrix, inhibit the recruitment and
function of osteoclasts and stimulate osteoblasts to produce an inhibitor of osteoclast
formation. (See: S. E. Papapoulos, *Medicina (Buenos Aires)* 57 (Suppl. I):61-64

(1997); and D. L. Lourwood, *Pharmacotherapy*, 18(4):779-789 (1998))

Bisphosphonates are resistant to metabolic and enzymatic inactivation by skeletal pyrophosphatases as they contain a phosphorous-carbon-phosphorous backbone rather than the phosphorous-oxygen-phosphorous backbone of pyrophosphates.

5 There are adverse side effects associated with bisphosphonate therapies such as nausea, vomiting, heartburn, diarrhea, gastrointestinal ulceration, osteomalacia, bone pain, increased fracturing, acute renal failure, hearing loss and toxic skin reactions are associated with the use of bisphosphonates. Generally, these adverse side effects are addressed by administering lower dosages, decreasing the frequency or periods of treatments and/or discontinuing therapy. Consequently, the lower
10 dosages and decreased treatments decrease the efficacy of bisphosphonate therapy. Furthermore, although bisphosphonates are efficacious in treating bony metastatic disease, they are not anticancer agents per se. Therefore, bisphosphonates alone are not effective in treating cancer, and rather are used to palliate symptoms such as pain.

15 Although, photodynamic therapy (PDT) has received increasing interest as a mode of treatment for a wide variety of different cancers, PDT for the treatment of metastatic bone disease is underdeveloped. Furthermore, PDT is often associated with inadvertent tissue damage normal tissue adjacent to diseased tissue to be treated. This inadvertent damage to collateral tissues is due to the nonspecific uptake of the
20 photosensitizer by tissue the photosensitizer perfuses. Thus, a non-specific uptake of photosensitizer by bone tissue during PDT could potentially damage normal bone tissue that has been replaced by the abnormal bone formation associated with a particular disorder such as Paget's Disease.

25 Clearly, the acknowledged side effects and probable lack of efficacy of the current PDT therapies against skeletal metastases present a need for a different approach for the treatment of metastatic bone diseases.

30 Citation of the above documents is not intended as an admission that any of the foregoing is pertinent prior art. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents. Further, all documents referred to throughout this application are incorporated in their entirety by reference herein.

SUMMARY OF THE INVENTION

The present disclosure teaches compositions and methods for treating metabolic bone disorders and bone metastases.

5 The present invention relates to bisphosphonate conjugates or pyrophosphate conjugates and their administration for PDT treatment of metabolic bone disorders and metastases.

Specifically, the present invention relates to the treatment of metabolic bone disorders and metastases by the precise targeting of photosensitive agents or other energy activated agents, drugs and compounds to the target pathologic bone cells or pathologic bone tissues or skeletal metastases due to cancer of a mammalian subject, and activating these targeted photosensitizers by subsequently administering to the subject light or ultrasonic energy of a relatively low fluence rate over a prolonged period of time from a light or ultrasonic energy source that is either external or internal to the target tissues in order to achieve maximal cytotoxicity with minimal side effects.

One embodiment of the present invention is drawn to compositions comprising photosensitive agents conjugated to a compound selected from the group consisting of: bisphosphonates; pyrophosphonates; thiobisphosphonates; and nitrobisphosphonates. The photosensitizing agent is selected from the group consisting of: indocyanine green (ICG); methylene blue; toluidine blue; aminolevulinic acid (ALA); chlorin compounds; phthalocyanines; porphyrins; purpurins; texaphyrins; and any other agent that absorbs light in a range of 500 nm - 1100 nm. A preferred embodiment of this invention contemplates that the photosensitizing agent is indocyanine green (ICG) and the compound conjugated to ICG is a bisphosphonate. These conjugates may be further conjugated to another ligand where the ligand is a target tissue specific antibody, peptide or polymer.

Another embodiment of the present invention is drawn to methods of using these bisphosphonate compositions in PDT of diseased tissues related metabolic bone disorders and bone metastases due to cancer. These methods generally comprise: administering to the subject a therapeutically effective amount of a bisphosphonate composition, where the bisphosphonate composition selectively binds to the pathologic target tissue. This step is followed by irradiating at least a portion of the subject with light at a wavelength or waveband absorbed by the bisphosphonate

composition, where the light is provided by a light source, and where the irradiation is at a relatively low fluence rate that results in the activation of the bisphosphonate composition. In this embodiment of the present invention, the bisphosphonate composition is cleared from non-target tissues of the subject prior to irradiation.

5 A further embodiment of the present invention is drawn to the method as described above, and includes the steps of imaging the target tissue and determining the sites of irradiation.

Another embodiment of the present invention is drawn to a method of PDT of a target tissue in a mammalian subject as described above, where the light source is external to the patient's intact skin layer. A further embodiment of this invention is drawn to this method of PDT wherein the light source is inserted underneath the patient's intact skin layer, but is external to an intact organ surface, where the organ comprises the target tissue. Still a further embodiment of the present invention of PDT contemplates that the light source is inserted underneath the patient's intact skin layer and is inserted into an organ, where the organ comprises the target tissue.

Another preferred embodiment contemplates a transcutaneous PDT method where the photosensitizing agent delivery system comprises a liposome delivery system consisting essentially of bisphosphonate compositions.

20 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the structure of bisphosphonates; including: etidronate; pamidronate; risedronate; clodronate; alendronate; ibandronate and tiludronate.

Figure 2 shows the structure of pyrophosphate.

Figure 3 shows the structure of nitrobisphosphonates and thiobisphosphonates.

25

DETAILED DESCRIPTION OF THE INVENTION

This invention provides compositions and methods for treating diseased tissues related to metabolic bone disorders and metastases in mammalian subjects. The compositions are bisphosphonates, pyrophosphates or bisphosphonate-like compounds conjugated to photosensitive agents which are optionally further conjugated to ligands which are target tissue specific antibodies, peptides or polymers.

30

The methods of PDT treatment utilize these compositions to target the tissues

or cells of a mammalian subject to be treated. The methods comprise irradiating at least a portion of the subject with light at a wavelength or waveband absorbed by said photosensitizing agent that under conditions of activation during photodynamic therapy using a relatively low fluence rate, but an overall high total fluence dose
5 resulting in minimal collateral normal tissue damage.

Generally, PDT is performed by first administering a photosensitive compound systemically or topically, followed by illumination of the treatment site at a wavelength or waveband which closely matches the absorption spectra of the photosensitizer. In doing so, singlet oxygen and other reactive species are generated
10 leading to a number of biological effects resulting in cytotoxicity. The depth and volume of the cytotoxic effect in tissue depends on the complex interactions of light penetration in tissue, the photosensitizer concentration and cellular location, and availability of molecular oxygen.

Terms as used herein are based upon their art recognized meaning and from
15 the present disclosure should be clearly understood by the ordinary skilled artisan. For sake of clarity, terms may also have particular meaning as would be clear from their use in context. For example, transcutaneous more specifically herein refers to the passage of light through unbroken tissue. Where the tissue layer is skin or dermis, transcutaneous includes transdermal and the light source is external to the outer skin
20 layer. Transillumination refers herein to the passage of light through a tissue layer, such as the outer ocortex layer of an organ such as bone, where the light source is external to the organ, but internal or implanted into the subject or patient.

Specifically, the present invention is based on the precise targeting of photosensitive agents or drugs and compounds to specific target antigens of a subject
25 or patient and to the method of activation of targeted photosensitizer agents by subsequently administering to the subject light of a relatively low fluence rate over a prolonged period of time from a light source that is external to the target tissue in order to achieve maximal cytotoxicity with minimal side effects or collateral tissue damage.

30 Further, as used herein "target cells" or "target tissues" are those cells or tissues, respectively that are intended to be impaired or destroyed by this treatment method. Target cells or target tissues take up the photosensitizing agent; then when sufficient radiation is applied, these cells or tissues are impaired or destroyed. Target

cells are those cells in target tissues related to those involved in metabolic bone disorders and bone metastases. Also included among target cells are cells undergoing rapid division as compared to non-target cells. The term "target cells" also includes, but is not limited to, microorganisms such as bacteria, viruses, fungi, parasites and other infectious agents which may be infecting a bony tissue. Thus, the term "target cell" is not limited to living cells but also includes infectious particles such as viruses.

"Non-target cells" are all the cells of an intact animal which are not intended to be impaired or destroyed by the treatment method. These non-target cells include but are not limited to healthy bone cells, and other normal bone tissue, not otherwise identified to be targeted.

"Destroy" is used to mean kill the desired target cell. "Impair" means to change the target cell in such a way as to interfere with its function. "Photosensitive agent" is a chemical compound which when contacted by radiation, absorbs the light, which results in impairment or destruction of the target cells. Virtually any chemical compound that homes to a selected target and absorbs light may be used in this invention. Preferably, the chemical compound is nontoxic to the animal to which it is administered or is capable of being formulated in a nontoxic composition. Preferably, the chemical compound in its photodegraded form is also nontoxic. A comprehensive listing of photosensitive chemicals may be found in Kreimer-Birnbaum, Sem. Hematol. 26:157-73, 1989.

Photosensitive compounds include, but are not limited to, chlorins, bacteriochlorins, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens, benzoporphyrin derivatives (BPD) and porfimer sodium and pro-drugs such as delta-aminolevulinic acid, which can produce drugs such as protoporphyrin. Other compounds include indocyanine green (ICG); methylene blue; toluidine blue; texaphyrins; and any other agent that absorbs light in a range of 500 nm - 1100 nm.

Bisphosphonates, pyrophosphates and bisphosphonate-like compounds, collectively referred to herein as "bisphosphonates" are those compounds exhibiting the characteristics of compounds having a phosphate-oxygen-phosphate or phosphate-carbon-phosphate backbone which characteristics comprise the ability to bind strongly calcium crystals and affect osteoclast-mediated bone resorption. Examples of such bisphosphonates are, but are not limited to, etidronate, tiludronate, clodronate, pamidronate, alendronate, risedronate and ibandronate.

"Bisphosphonate compositions" are photosensitive agents conjugated to bisphosphonates, pyrophosphates, nitrobisphosphonates, thiobisphosphonates or other compounds having similar bisphosphonate-like properties and that also possess either an oxygen or carbon or nitrogen or sulfur atom bound to two phosphonate groups.

5 "Nitrobisphosphonates" are compounds comprising a nitrogen atom bound to two phosphonate groups.

"Thiobisphosphonates" are compounds comprising a sulfur atom bound to two phosphonate groups.

10 "Radiation" as used herein includes all wavelengths. Preferably, the radiation wavelength is selected to match the wave length(s) or wavebands which excites the photosensitive compound. Even more preferably, the radiation wavelength matches the excitation wavelength of the photosensitive compound and has low absorption by the non-target cells and the rest of the intact animal, including blood proteins. For example, the preferred wavelength for ICG is the range of 750-850 nm.

15 The radiation is further defined in this invention by its intensity, duration, and timing with respect to dosing with the photosensitive agent. The intensity or fluence rate must be sufficient for the radiation to penetrate skin and reach the target cells, target tissues or target compositions. The total fluence dose must be sufficient to photoactivate enough photosensitive agent to act on the target cells. Both intensity and duration must be limited to avoid overtreating the animal. Timing with respect to dosing with the photosensitive agent is important, because 1) the administered photosensitive agent requires some time to home in on target cells and 2) the blood level of many photosensitive agents decreases rapidly with time.

20 This invention provides a method of treating an animal, which includes, but is not limited to, humans and other mammals. The term "mammals" or "mammalian subject" also includes farm animals, such as cows, hogs and sheep, as well as pet or sport animals such as horses, dogs and cats.

25 By "intact animal" is meant that the whole, undivided animal is available to be exposed to radiation. No part of the animal is removed for separate radiation, in contrast with photophoresis, in which the animal's blood is circulated outside its body for exposure to radiation. The entire animal need not be exposed to radiation. Only a portion of the intact animal subject may or need be exposed to radiation.

30 "Transcutaneously" is used herein as meaning through the skin of an animal

subject.

Briefly, a bisphosphonate composition incorporating a photosensitizing agent is generally administered to the animal before the animal is subjected to radiation.

Preferred photosensitizing agents include, but are not limited to, chlorins, bacteriochlorins, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens and pro-drugs such as .delta.-aminolevulinic acid, which can produce drugs such as protoporphyrin. More preferred are: methylene blue; toluidine blue; texaphyrins; and any other agent that absorbs light in a range of 500 nm -1100 nm. Most preferred is indocyanine green (ICG) (for example, see: WO 92/00106 (Raven *et al.*); WO97/31582 (Abels *et al.*) and Devoisselle *et al.*, SPIE 2627:100-108, 1995).

The bisphosphonate composition is administered locally or systemically. The bisphosphonate composition is administered orally or by injection which may be intravenous, subcutaneous, intramuscular or intraperitoneal. The photosensitizing agent and/or a bisphosphonate composition also can be administered enterally or topically via patches or implants.

The bisphosphonate composition also can be conjugated to specific ligands reactive with a target, such as receptor-specific ligands or immunoglobulins or immunospecific portions of immunoglobulins, permitting them to be more concentrated in a desired target cell or microorganism. The photosensitizing agent and/or a bisphosphonate composition may be further conjugated to a ligand-receptor binding pair, which includes, but is not limited to: biotin-streptavidin; chemokine-chemokine receptor; growth factor-growth factor receptor; and antigen-antibody. This conjugation may permit lowering of the required dose level since the material is more selectively target and less is wasted in distribution into other tissues whose destruction must be avoided.

The bisphosphonate composition may also be conjugated to "imaging agents" such as technetium, radium, indium or gallium.

The bisphosphonate composition can be administered in a dry formulation, such as pills, capsules, suppositories or patches. The bisphosphonate composition also may be administered in a liquid formulation, either alone with water, or with pharmaceutically acceptable excipients, such as are disclosed in Remington's Pharmaceutical Sciences. The liquid formulation also can be a suspension or an emulsion. Liposomal or lipophilic formulations may be desirable. If suspensions or

emulsions are utilized, suitable excipients include water, saline, dextrose, glycerol, and the like. These compositions may contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, antioxidants, pH buffering agents, and the like.

5 The dose of bisphosphonate composition will vary with the target cell(s) sought, the optimal blood level (see Example 1), the animal's weight and the timing of the irradiation. Depending on the bisphosphonate composition used, an equivalent optimal therapeutic level will have to be established. Preferably, the dose is calculated to obtain a blood level between about 0.001 and 100 $\mu\text{g/ml}$. Preferably, the dose will
10 obtain a blood level between about 0.01 and 10 $\mu\text{g/ml}$.

 The methods comprise irradiating at least a portion of the subject with light at a wavelength or waveband absorbed by said photosensitizing agent that under conditions of activation during photodynamic therapy using a relatively low fluence rate, but an overall high total fluence dose resulting in minimal collateral normal
15 tissue damage. What is meant by "relatively low fluence rate" is a fluence rate that is lower than that typically used and one that generally does not result in significant damage to collateral or non-target tissues. Specifically, the intensity of radiation used to treat the target cell or target tissue is preferably between about 5 and 100 mW/cm^2 .
20 More preferably, the intensity of radiation is between about 10 and 75 mW/cm^2 . Most preferably, the intensity of radiation is between about 15 and 50 mW/cm^2 .

 The duration of radiation exposure is preferably between about 30 minute and 72 hours. More preferably, the duration of radiation exposure is between about 60 minutes and 48 hours. Most preferably, the duration of radiation exposure is between about 2 hours and 24 hours.

25 While not wishing to be limited by a theory, the inventor proposes that a photosensitizer agent can be substantially and selectively photoactivated in the target cells and target tissues within a therapeutically reasonable period of time and without excess toxicity or collateral damage to non-target tissues. Thus, there appears to be a therapeutic window bounded by the photosensitizer agent dosage and radiation
30 dosage. The formation of photodegradation products of a photosensitizer agent was used as an indicator of photoactivation. Photoactivation of a photosensitizer agent has been postulated to cause the formation of singlet oxygen, which has a cytotoxic effect. In view of the problems related to current methods of treating skeletal metastases

which are palliative, the envisaged method of targeted transcutaneous PDT of patients injected with a biphosphonate composition and subjected to a relatively low fluence rate, but high total fluence dose of irradiation is an attractive approach to the treatment of target tissues, that include neoplastic disease and infectious agents.

5 Additionally, the present invention is drawn to a method for transcutaneous therapy of skeletal metastases in a mammalian subject or patient by first administering to the subject a therapeutically effective amount of a first conjugate comprising a first member of a ligand-receptor binding pair conjugated to an antibody or antibody fragment, wherein said antibody or antibody fragment selectively binds to a target
10 tissue antigen; and simultaneously or subsequently administering to the subject a therapeutically effective amount of a second conjugate comprising a second member of the ligand-receptor binding pair conjugated to an biphosphonate composition or biphosphonate agent delivery system wherein the first member binds to the second member of the ligand-receptor binding pair. These steps are followed by irradiating
15 or sonicating at least a portion of the subject with energy at a wavelength, waveband, or frequency absorbed by said biphosphonate composition or biphosphonate agent delivery system, by the product thereof, wherein said energy is provided by an energy source that is external to the subject; and wherein said light irradiation or sonication is at a low dose rate that results in the activation of said biphosphonate composition or
20 biphosphonate agent delivery system

 While the preferred embodiment of the present invention is drawn to the use of light energy in a photodynamic therapy of skeletal tumors other forms of energy are within the scope of this invention and understandable by one of ordinary skill in the art. Such forms of energy include, but are not limited to: thermal; ultrasonic;
25 ultrasonic; chemical; photo or light; microwave; ionizing, such as: x-ray, and gamma ray;; and electrical. For example, sonodynamically induced or activated biphosphonate compositions include, but are not limited to: gallium-porphyrin complex (see: Yumita *et al.*, *Cancer Letters*, 112: 79-86, 1997); other porphyrin complexes, such as protoporphyrin and hematoporphyrin (see: Umemura *et al.*,
30 *Ultrasonics Sonochemistry* 3: S187-S191, 1996); other cancer drugs, such as daunorubicin and adriamycin, used in the presence of ultrasound therapy (see: Yumita *et al.*, *Japan J. Hyperthermic Oncology*, 3(2): 175-182, 1987).

This invention further contemplates the use of an energy source, preferably a light source, that is external to the target tissue. The target tissues may include and may relate to cells and tissues involved in metabolic bone disorders and metastases, per se.

5 The ordinary skilled artisan would be familiar with various ligand-receptor binding pairs, including those known and those currently yet to be discovered. Those known, include, but are not limited to the group consisting of: biotin-streptavidin; chemokine-chemokine receptor; growth factor-growth factor receptor; and antigen-antibody. This invention contemplates a preferred embodiment that includes the use
10 of biotin-streptavidin as the ligand-receptor binding pair. However, the ordinary skilled artisan would readily understand from the present disclosure that any ligand-receptor binding pair may be useful provided the ligand-receptor binding pair demonstrate a specificity for the binding by the ligand to the receptor and further provided that the ligand-receptor binding pair permit the creation of a first conjugate
15 comprising a first member of the ligand-receptor binding pair conjugated to an antibody or antibody fragment, wherein said antibody or antibody fragment selectively binds to a target tissue antigen; and further permit the creation of a second biphosphonate conjugate comprising a second member of the ligand-receptor binding pair conjugated to a photosensitizing agent or ultrasound sensitive agent, and further
20 wherein the first member binds to the second member of the ligand-receptor binding pair.

A preferred embodiment of the present invention is drawn to a method where the photosensitizing agent delivery system includes a liposome delivery system consisting essentially of the bisphosphonate composition. A still further and preferred
25 embodiment of the present invention contemplates the disclosed method where the photosensitizing agent delivery system utilizes both a liposome delivery system and a bisphosphonate composition, where each is separately conjugated to a second member of the ligand-receptor binding pair, and where the first member binds to the second member of the ligand-receptor binding pair, and more preferably where the ligand-receptor binding pair is biotin-streptavidin. This embodiment further contemplates
30 that the bisphosphonate composition as well as the photosensitizing agent delivery system may both be specifically targeted through the selective binding to a target tissue antigen by the antibody or antibody fragment of the first member binding pair.

Such dual targeting is envisioned to enhance the specificity of uptake and to increase the quantity of uptake. Though the total fluence delivered to the treatment site will be variable depending on the size and nature of the treatment site, it is contemplated that the preferred total fluence delivered either internally or from an external light source will range between 30 Joules to 25,000 Joules, more preferably between 100 Joules to 20,000 Joules, and most preferably between 500 Joules to 10,000 Joules.

Having now generally described the invention, the same will be more readily understood through reference to the following examples which are provided by way of illustration, and are not intended to be limiting of the present invention, unless specified.

EXAMPLE 1

Photodynamic Therapy of Treating or Preventing Bone Metastases

A. A patient having or susceptible to bone metastases is given an oral or intravenous dose of a photosensitizer agent, indocyanine green (ICG), conjugated to a bisphosphonate which specifically binds the target tissue. One or more light sources are strategically placed or implanted near the tissue to be treated. Following a sufficient amount of time to permit clearing of the bisphosphonate composition from the non-target tissues, the light sources are activated, irradiating the target tissue with a relatively low fluence rate, but high total fluence dose of light in the wavelength from about 750 nm to about 850 nm. The light may be applied internally or from an external allocation, with the light effectively penetrating the skin and intervening tissue due to its long wavelength.

The specific dose of biphosphonate conjugate is that which results in a concentration of active ICG sufficient to obtain a blood level between about 0.001 and 100 $\mu\text{g/ml}$. and more preferably, a dose of between about 0.01 and 10 $\mu\text{g/ml}$. However, it is well within the skill of the ordinary skilled artisan to determine the specific therapeutically effective dose using standard clinical practices and procedures.

Additionally, as renal clearance is the only route of bisphosphonate elimination, and the amount of bisphosphonates not absorbed into bone tissue is excreted unchanged in urine, the specific therapeutically effective dose may be

customized for an individual subject undergoing treatment by monitoring the urine levels of bisphosphonates.

Similarly, the specific fluence rate and total fluence dose may be routinely determined from the disclosure herein.

5 Furthermore, as most urinary excretion of bisphosphonates occurs within 12 hours of administration and little additional drug is recovered in the urine after 24 hours, the sufficient amount of time to permit clearing of the bisphosphonate composition from the non-target tissues preferred is 12-15 hours after administration of the bisphosphonate composition.

10

B. Alternatively, the bisphosphonate composition above could be further conjugated to an imaging agent such as technetium. Thus, the method as disclosed in A above could further comprise the steps of performing a nuclear medicine scan and imaging the metastatic sites to be treated.

15

C. The method as disclosed in A could further comprise the steps of administering a composition comprising bisphosphonate conjugated to an imaging agent such as technetium, performing a nuclear medicine scan and imaging the metastatic sites to be treated.

20

EXAMPLE 2

Photodynamic Therapy of Paget's Disease

As Paget's Disease is characterized by localized enhancement of osteoclastic activity and greater numbers of large osteoclasts, this disorder may be treated
25 effectively with the PDT methods as described above. For example, a mammalian subject suffering from Paget's Disease is given an oral or intravenous dose of a photosensitizer agent, such as indocyanine green (ICG), conjugated to a bisphosphonate which selectively localizes to the sites osteoclastic activity. The bisphosphonate composition is further conjugated to an imaging agent, such as
30 technetium, or another bisphosphonate composition conjugated to an imaging agent is also administered to the subject. Following a sufficient amount of time to permit clearing of the bisphosphonate composition from the non-target tissues, a nuclear

medicine scan is then performed in order to determine the sites of abnormal osteoclastic activity and target the great numbers of large osteoclasts.

Then one or more light sources are strategically placed or implanted near the tissue to be treated, the light sources are activated, irradiating the target tissue with a
5 relatively low fluence rate, but high total fluence dose of light in the wavelength from about 750 nm to about 850 nm. The light may be applied internally or externally.

The specific dose of photosensitizer conjugate is that which results in a concentration of active ICG sufficient to obtain a blood level between about 0.001 and 100 µg/ml. and more preferably, a dose of between about 0.01 and 10 µg/ml.
10 However, it is well within the skill of the ordinary skilled artisan to determine the specific therapeutically effective dose using standard clinical practices and procedures.

Additionally, as renal clearance is the only route of bisphosphonate elimination, and the amount of bisphosphonates not absorbed into bone tissue is
15 excreted unchanged in urine, the specific therapeutically effective dose may be customized for an individual subject undergoing treatment by monitoring the urine levels of bisphosphonates.

Similarly, the specific fluence rate and total fluence dose may be routinely determined from the disclosure herein.

20 Furthermore, as most urinary excretion of bisphosphonates occurs within 12 hours of administration and little additional drug is recovered in the urine after 24 hours, the sufficient amount of time to permit clearing of the bisphosphonate composition from the non-target tissues preferred is 12-15 hours after administration of the bisphosphonate composition.

25 As Paget's Disease is characterized by abnormally localized enhanced osteoclastic activity followed by abnormal bone formation of poor structural quality, this type of PDT treatment should minimize the bone pain, skeletal deformity, fractures, secondary arthritis, neurologic impairment and hearing loss. Since increased bone turnover is associated with increased serum levels of alkaline
30 phosphatase and increased urinary excretion of hydroxyproline, deoxypyridinoline and cross-linked *N*-telopeptide of type I collagen, the efficacy of the treatment may be determined by the serum levels of alkaline phosphatase and/or the urine levels of hydroxyproline, deoxypyridinoline and cross-linked *N*-telopeptide of type I collagen.

Usually, the success of the treatment is estimated by evaluating whether serum alkaline phosphatase has been reduced by 60% or lowered into the normal ranges.

EXAMPLE 3

Photodynamic Therapy of Hypercalcemia

5 If hypercalcemia in a subject results from the direct or indirect effect of tumor cells on bone resorption, PDT treatment may be effective in returning serum calcium levels to normal and reducing bone pain. For example, a mammalian subject suffering from hypercalcemia is given an oral or intravenous dose of a photosensitizer agent, such as indocyanine green (ICG), conjugated to a bisphosphonate which
10 selectively localizes to the tumor cells on the bone and/or the osteoclasts activated by tumor cells. The bisphosphonate composition is further conjugated to an imaging agent, such as technetium, or another bisphosphonate composition conjugated to an imaging agent is also administered to the subject. Following a sufficient amount of time to permit clearing of the bisphosphonate composition from the non-target tissues,
15 a nuclear medicine scan is then performed in order to determine the sites of the tumor cells on the bone and/or the osteoclasts activated by tumor cells.

Then one or more light sources are strategically placed or implanted near the tissue to be treated, the light sources are activated, irradiating the target tissue with a relatively low fluence rate, but high total fluence dose of light in the wavelength from
20 about 750 nm to about 850 nm. The light may be applied internally or externally.

The specific dose of photosensitizer conjugate is that which results in a concentration of active ICG sufficient to obtain a blood level between about 0.001 and 100 µg/ml. and more preferably, a dose of between about 0.01 and 10 µg/ml. However, it is well within the skill of the ordinary skilled artisan to determine the
25 specific therapeutically effective dose using standard clinical practices and procedures.

Additionally, as renal clearance is the only route of bisphosphonate elimination, and the amount of bisphosphonates not absorbed into bone tissue is excreted unchanged in urine, the specific therapeutically effective dose may be
30 customized for an individual subject undergoing treatment by monitoring the urine levels of bisphosphonates.

Similarly, the specific fluence rate and total fluence dose may be routinely determined from the disclosure herein.

Furthermore, as most urinary excretion of bisphosphonates occurs within 12 hours of administration and little additional drug is recovered in the urine after 24 hours, the sufficient amount of time to permit clearing of the bisphosphonate composition from the non-target tissues preferred is 12-15 hours after administration of the bisphosphonate composition.

As hypercalcemia is characterized by abnormally high serum calcium levels, this type of PDT treatment should minimize the associated complications of hypercalcemia such as intense pain, pathologic fractures, changes in normal neurologic and cardiac function, coma, arrhythmias and death. Additionally, the success of the treatment may be evaluated by the amount of serum calcium levels.

EXAMPLE 4

Photodynamic Therapy of Type I Osteoporosis

As Type I osteoporosis is characterized by increased osteoclastic activity followed by accelerated bone resorption, this disorder may be treated effectively with the PDT methods as described above. For example, a mammalian subject suffering from Type I osteoporosis is given an oral or intravenous dose of a photosensitizer agent, such as indocyanine green (ICG), conjugated to a bisphosphonate which selectively localizes to the sites osteoclastic activity. One or more light sources are strategically placed or implanted near the tissue to be treated. Following a sufficient amount of time to permit clearing of the bisphosphonate composition from the non-target tissues, the light sources are activated, irradiating the target tissue with a relatively low fluence rate, but high total fluence dose of light in the wavelength from about 750 nm to about 850 nm. The light may be applied internally or externally.

The specific dose of photosensitizer conjugate is that which results in a concentration of active ICG sufficient to obtain a blood level between about 0.01 and 100 $\mu\text{g/ml}$. and more preferably, a dose of between about 0.01 and 10 $\mu\text{g/ml}$. However, it is well within the skill of the ordinary skilled artisan to determine the specific therapeutically effective dose using standard clinical practices and procedures.

Additionally, as renal clearance is the only route of bisphosphonate elimination, and the amount of bisphosphonates not absorbed into bone tissue is excreted unchanged in urine, the specific therapeutically effective dose may be

customized for an individual subject undergoing treatment by monitoring the urine levels of bisphosphonates.

Similarly, the specific fluence rate and total fluence dose may be routinely determined from the disclosure herein.

5 Furthermore, as most urinary excretion of bisphosphonates occurs within 12 hours of administration and little additional drug is recovered in the urine after 24 hours, the sufficient amount of time to permit clearing of the bisphosphonate composition from the non-target tissues preferred is 12-15 hours after administration of the bisphosphonate composition.

10 Since increased bone turnover is associated with increased serum levels of alkaline phosphatase and increased urinary excretion of hydroxyproline, deoxypyridinoline and cross-linked *N*-telopeptide of type I collagen, the efficacy of the treatment may be determined by the serum levels of alkaline phosphatase and/or the urine levels of hydroxyproline, deoxypyridinoline and cross-linked *N*-telopeptide
15 of type I collagen. Usually, the success of the treatment is estimated by evaluating whether serum alkaline phosphatase has been reduced by 60% or lowered into the normal ranges.

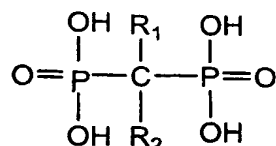
20 This invention has been described by a direct description and by examples. As noted above, the examples are meant to be only examples and not to limit the invention in any meaningful way. Additionally, one having ordinary skill in the art to which this invention pertains in reviewing the specification and claims which follow would appreciate that there are equivalents to those claimed aspects of the invention.
25 The inventors intend to encompass those equivalents within the reasonable scope of the claimed invention.

CLAIMS

1. A pharmaceutical composition comprising a photosensitizer agent conjugated to a compound selected from the group consisting of: bisphosphonates; pyrophosphonates; thiobisphosphonates; and nitrobisphosphonates.

2. The composition of claim 1 wherein the photosensitizer agent is selected from the group consisting of chlorins, bacteriochlorins, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens, benzoporphyrin derivatives (BPD), porfimer sodium, delta-aminolevulinic acid, protoporphyrin, indocyanine green (ICG), methylene blue, toluidine blue, texaphyrins and any other agent that absorbs light in a range of 500 nm - 1100 nm.

3. The composition of claim 1 wherein the compound is a bisphosphonate of the formula



wherein R¹ is independently selected from the group consisting of: hydroxyl, an amino group, -CN, -NO₂, haloalkyl, heteroaryl, phenyl, alkyl, alkoxy, alkylthio, halo and alkyl-carbonyloxy; and wherein R² is independently selected from the group consisting of: alkyl, aminoalkyl -CN, -NO₂, -NH₂, haloalkyl, heteroaryl, phenyl, alkyl, alkoxy, alkylthio, halo and alkyl-carbonyloxy.

4. The composition of claim 3 wherein R¹ is hydroxyl or an amino group and R² is alkyl or aminoalkyl.

5. The composition of claim 3 wherein the compound is selected from the group consisting of etidronate, tiludronate, clodronate, pamidronate, alendronate, risedronate and ibandronate.

6. The composition of claim 1 further conjugated to a target tissue

specific ligand.

7. The composition of claim 1 further conjugated to an imaging agent.

5 8. A method for destroying or impairing target cells involved in disease of bone tissue in a mammalian subject comprising:

administering to the subject a therapeutically effective amount of the composition of any one of claims 1 to 7, wherein said composition selectively binds the target cells or target tissues involved in the disease of bone tissue; and

10 irradiating at least a portion of the subject with light at a wavelength or waveband absorbed by said composition, wherein said light is provided by a light source, and wherein said irradiation is at a relatively low fluence rate that results in the activation of said composition; and

15 wherein said composition is cleared from non-target tissues of the subject prior to said irradiation.

9. The method of claim 8, wherein said disease of bone tissue is a metabolic bone disorder or bone metastases.

20 10. The method of claim 8 wherein said composition is conjugated to an imaging agent.

25 11. The method of claim 10 further comprising the steps of performing a nuclear medicine scan and imaging the target cells or target tissues to be destroyed or impaired.

12. The method of claim 8, wherein said composition is conjugated to a ligand that specifically binds to target cells or target tissues.

30 13. A method for destroying or impairing target cells involved in disease of bone tissue in a mammalian subject comprising:

administering to the subject a therapeutically effective amount of a composition comprising a photosensitizer agent conjugated to a compound selected

from the group consisting of: bisphosphonates; pyrophosphonates; thiobisphosphonates; and nitrobisphosphonates, wherein said composition selectively binds the target cells or target tissues involved in said disease of bone tissue; and
irradiating at least a portion of the subject with light at a wavelength absorbed
by said composition, wherein said light is provided by a light source, and wherein said
irradiation is at a relatively low fluence rate that results in the activation of said
composition, wherein said composition is cleared from non-target tissues of the
subject prior to said irradiation.

14. The method of claim 13, wherein said disease of bone is a metabolic bone disorder or bone metastases.

15. A method for treating a metabolic bone disorder or bone metastases in a mammalian subject comprising:

administering to the subject a therapeutically effective amount of a composition comprising

a photosensitizer agent selected from the group consisting of chlorins, bacteriochlorins, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens, benzoporphyrin derivatives (BPD), porfimer sodium, delta-aminolevulinic acid, protoporphyrin, indocyanine green (ICG), methylene blue, toluidine blue, texaphyrins and any other agent that absorbs light in a range of 500 nm - 1100 nm

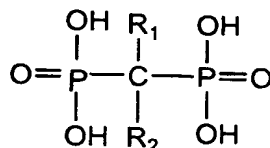
which is conjugated to a compound selected from the group consisting of: bisphosphonates; pyrophosphonates; thiobisphosphonates; and nitrobisphosphonates which selectively binds the target tissues or cells involved in the metabolic bone disorder or bone metastases and said composition is further conjugated to an imaging agent; and

performing a nuclear medicine scan;

imaging the target tissues or cells to be treated; and

irradiating at least a portion of the subject with light at a wavelength absorbed by said composition, wherein said light is provided by a light source, and wherein said irradiation is at a relatively low fluence rate that results in the activation of said composition, wherein said composition is cleared from non-target tissues of the subject prior to said irradiation.

16. A method for destroying or impairing target cells involved in disease of bone tissue in a mammalian subject according to claim 13 or 15, wherein said compound is a bisphosphonate of the formula



wherein R¹ is independently selected from the group consisting of: hydroxyl, an amino group, -CN, -NO₂, haloalkyl, heteroaryl, phenyl, alkyl, alkoxy, alkylthio, halo and alkyl-carbonyloxy; and wherein R² is independently selected from the group consisting of: alkyl, aminoalkyl -CN, -NO₂, -NH₂, haloalkyl, heteroaryl, phenyl, alkyl, alkoxy, alkylthio, halo and alkyl-carbonyloxy.

17. The method according to claim 13 or 15, wherein R¹ is hydroxyl or an amino group and R² is alkyl or aminoalkyl.

18. A method according to claim 13 or 15, wherein the compound is selected from the group consisting of etidronate, tiludronate, clodronate, pamidronate, alendronate, risedronate and ibandronate.

19. A method according to claim 13 or 15, wherein the composition is conjugated to a target tissue specific ligand or an imaging agent.

20. A method for destroying or impairing target cells involved in disease of bone tissue in a mammalian subject comprising:

administering to the subject a therapeutically effective amount of a composition comprising a photosensitizer agent, wherein said agent is selected from the group consisting of chlorins, bacteriochlorins, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens, benzoporphyrin derivatives (BPD), porfimer sodium, delta-aminolevulinic acid, protoporphyrin, indocyanine green (ICG), methylene blue, toluidine blue, texaphyrins and any other agent that absorbs light in a range of 600 nm - 1100 nm, and wherein said agent is conjugated to a compound

selected from the group consisting of: bisphosphonates; pyrophosphonates; thiobisphosphonates; and nitrobisphosphonates; and wherein said composition selectively binds the target cells or target tissues involved in said disease of bone tissue; and

5 irradiating at least a portion of the subject with light at a wavelength absorbed by said composition, wherein said light is provided by a light source, and wherein said irradiation is at a relatively low fluence rate that results in the activation of said composition; and

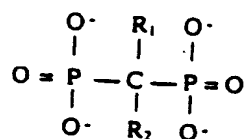
10 wherein said composition is cleared from non-target cells or non-target tissues of the subject prior to said irradiation.

21. The method of claim 20, wherein said disease of bone tissue is a metabolic bone disorder or bone metastases.

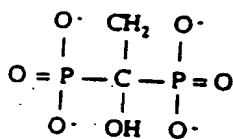
15 22. The method of any one of claims 8-21, wherein said fluence rate results in the irradiating of said subject with a total fluence of irradiation delivered either internally or from an external light source at a range of about between 30 Joules/cm² to 25,000 Joules/cm².

20 23. The method of claim 22, wherein said range is between 100 Joules/cm² to 20,000 Joules/cm².

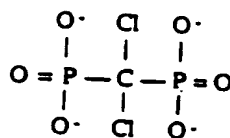
24. The method of claim 23, wherein said range is between 500 Joules/cm² to 10,000 Joules/cm².



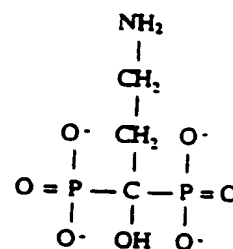
Bisphosphonate



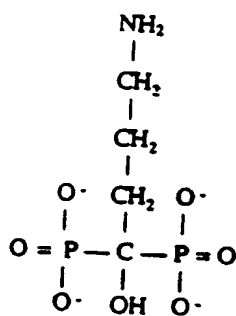
Etidronate



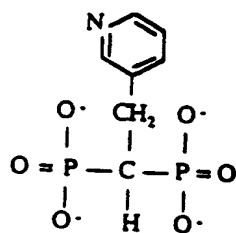
Clodronate



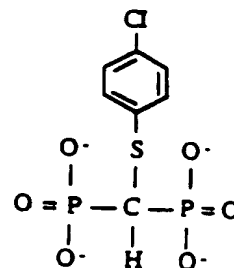
Pamidronate



Alendronate

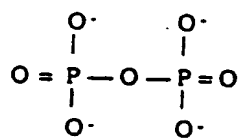


Risedronate



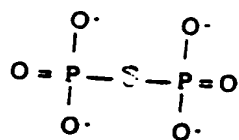
Tiludronate

Figure 1

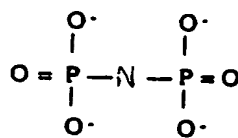


Pyrophosphate

Figure 2



Thiobisphosphonate



Nitrobisphosphonate

Figure 3

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
20 July 2000 (20.07.2000)

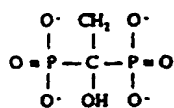
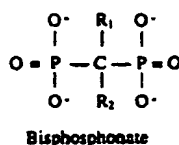
PCT

(10) International Publication Number
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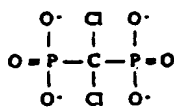
- (51) International Patent Classification⁷: A61K 41/00 (74) Agents: MAYS, Thomas, D. et al.; Morrison & Foerster LLP, 2000 Pennsylvania Avenue, N.W., Washington, DC 20006-1888 (US).
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- (71) Applicant (*for all designated States except US*): LIGHT SCIENCES, LTD. [US/US]; No. E-5, 1065 12th Avenue, N.W., Issaquah, WA 98027 (US).
- (72) Inventor; and
- (75) Inventor/Applicant (*for US only*): CHEN, James [US/US]; 2011-87th Place, N.E., Bellevue, WA 98004 (US).
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- Published:
— With international search report.

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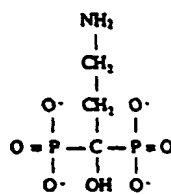
(54) Title: THERAPEUTIC COMPOSITIONS FOR METABOLIC BONE DISORDERS OR BONE METASTASES



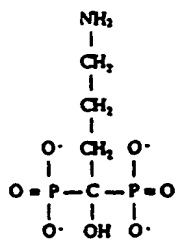
Etidronate



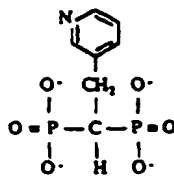
Clodronate



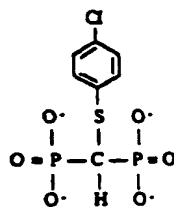
Pamidronate



Alendronate



Risedronate



Tiludronate

(57) Abstract: The present invention is drawn to methods and compositions useful for targeting and treating target tissues affected by or involved in metabolic bone disorders and bone metastases with photodynamic therapy (PDT) in a mammalian subject. The compositions are bisphosphonates, pyrophosphates or bisphosphonate-like compounds conjugated to photosensitive agents which are optionally further conjugated to ligands which are target tissue specific antibodies, peptides or polymers. The methods of PDT treatment utilize these compositions to target the tissues or cells of a mammalian subject to be treated. The methods comprise irradiating at least a portion of the subject with light at a wavelength absorbed by said photosensitizing agent that under conditions of activation during photodynamic therapy using a relatively low fluence rate, but an overall high total fluence dose results in minimal collateral tissue damage.

WO 00/41725 A3



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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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International Application No

PCT/US 00/00848

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K41/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EMBASE, BIOSIS, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 494 793 A (SCHINDELE DEBORAH C ET AL) 27 February 1996 (1996-02-27) abstract; claims 1,4 ---	1-7
Y	US 5 543 514 A (KRAL VLADIMIR ET AL) 6 August 1996 (1996-08-06) column 5, line 40 - line 42; claims ---	1-20
X	US 5 565 552 A (CROFTS SHAUN P ET AL) 15 October 1996 (1996-10-15) claims --- -/--	1-7

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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International Application No

PCT/US 00/00848

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MEEROVICH, GENNADY A. ET AL: "Photosensitizer for PDT based on phosphonate phthalocyanine derivative" retrieved from STN Database accession no. 126:115157 XP002141100 abstract & PROC. SPIE-INT. SOC. OPT. ENG. (1996), 2924(PHOTOCHEMOTHERAPY: PHOTODYNAMIC THERAPY AND OTHER MODALITIES II), 86-90 ,</p>	1-7
X	<p style="text-align: center;">---</p> <p>SHARMAN, WESLEY M. ET AL: "Novel water-soluble phthalocyanines substituted with phosphonate moieties on the benzo rings" TETRAHEDRON LETT. (1996), 37(33), 5831-5834 , XP002141099</p>	1-20
Y	<p>page 5833, line 8</p>	1-20
X	<p style="text-align: center;">---</p> <p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; NEMOTO, R. (1) ET AL: "Inhibition by a new bisphosphonate (YM175) of bone resorption induced by the MBT-2 tumour of mice." retrieved from STN XP002141101</p>	1-7
Y	<p>abstract & BRITISH JOURNAL OF CANCER, (1993) VOL. 67, NO. 5, PP. 893-897. ,</p> <p style="text-align: center;">-----</p>	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. l. Application No

PCT/US 00/00848

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5494793 A	27-02-1996	US 4803170 A	07-02-1989
		US 5346670 A	13-09-1994
		AU 642396 B	21-10-1993
		AU 4216389 A	02-04-1990
		CA 1337754 A	19-12-1995
		EP 0434727 A	03-07-1991
		JP 4500516 T	30-01-1992
		WO 9002747 A	22-03-1990
		US 5135717 A	04-08-1992
		AT 98020 T	15-12-1993
		AU 636562 B	06-05-1993
		AU 1056888 A	15-07-1988
		DE 3788356 D	13-01-1994
		DE 3788356 T	23-06-1994
		EP 0335902 A	11-10-1989
		WO 8804777 A	30-06-1988
US 5543514 A	06-08-1996	US 5457195 A	10-10-1995
		US 5159065 A	27-10-1992
		AU 5364494 A	09-05-1994
		WO 9409003 A	28-04-1994
		US 5530123 A	25-06-1996
		US 5587478 A	24-12-1996
		US 5808059 A	15-09-1998
		US 5594136 A	14-01-1997
		US 5744302 A	28-04-1998
		US 5672490 A	30-09-1997
		AU 7173691 A	24-07-1991
		EP 0515395 A	02-12-1992
		WO 9109861 A	11-07-1991
		US 5302714 A	12-04-1994
US 5565552 A	15-10-1996	US 5567687 A	22-10-1996
		US 5559207 A	24-09-1996
		US 5451576 A	19-09-1995
		US 5252720 A	12-10-1993
		US 5633354 A	27-05-1997
		US 5837866 A	17-11-1998
		AU 709951 B	09-09-1999
		AU 3727095 A	09-04-1996
		CA 2200571 A	28-03-1996
		EP 0782579 A	09-07-1997
		FI 971176 A	19-05-1997
		JP 10508581 T	25-08-1998
		NO 971317 A	16-05-1997
		WO 9609315 A	28-03-1996
		US 5798491 A	25-08-1998
		US 5607924 A	04-03-1997
		US 5595726 A	21-01-1997
		AU 694737 B	30-07-1998
		AU 7052694 A	03-01-1995
		EP 0702685 A	27-03-1996
		JP 8511532 T	03-12-1996
		NZ 267864 A	24-10-1997
		US 6072038 A	06-06-2000
		US 5969111 A	19-10-1999
		CA 2164419 A	22-12-1994
		WO 9429316 A	22-12-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/00848

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5565552 A		US 5763172 A	09-06-1998
		US 5888997 A	30-03-1999
		US 5457183 A	10-10-1995
		US 5580543 A	03-12-1996
		US 5587371 A	24-12-1996
		US 5632970 A	27-05-1997
		US 5801229 A	01-09-1998
		AU 3436793 A	03-08-1993
		CA 2127530 A	22-07-1993
		EP 0623134 A	09-11-1994
		FI 943445 A	20-07-1994
		JP 7503009 T	30-03-1995
		NO 942719 A	19-09-1994
		NZ 246795 A	27-02-1996
		US 5994535 A	30-11-1999
		WO 9314093 A	22-07-1993
		US 5569759 A	29-10-1996
		US 5432171 A	11-07-1995
		US 5475104 A	12-12-1995
		US 5439570 A	08-08-1995
		US 5599923 A	04-02-1997
		US 5504205 A	02-04-1996
		US 5733903 A	31-03-1998
		US 6069140 A	30-05-2000